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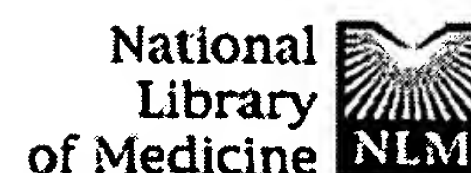
Identification and characterization of the T lymphocyte adhesion receptor for an alternative cell attachment domain (CS-1) in plasma fibronectin.

Wayner EA, Garcia-Pardo A, Humphries MJ, McDonald JA, Carter WG.

Fred Hutchinson Cancer Research Center, Seattle, Washington 98104.

Using mAb technology (Wayner, E. A., W. G. Carter, R. Piotrowicz, and T. J. Kunicki. 1988. J. Cell Biol. 107:1881-1891), we have identified a new fibronectin receptor that is identical to the integrin receptor alpha 4 beta 1. mAbs P3E3, P4C2, and P4G9 recognized epitopes on the alpha 4 subunit and completely inhibited the adhesion of peripheral blood and cultured T lymphocytes to a 38-kD tryptic fragment of plasma fibronectin containing the carboxy-terminal Heparin II domain and part of the type III connecting segment (IIICS). The ligand in IIICS for alpha 4 beta 1 was the CS-1 region previously defined as an adhesion site for melanoma cells. The functionally defined mAbs to alpha 4 partially inhibited T lymphocyte adhesion to intact plasma fibronectin and had no effect on their attachment to an 80-kD tryptic fragment containing the RGD (arg-gly-asp) adhesion sequence. mAbs (P1D6 and P1F8) to the previously described fibronectin receptor, alpha 5 beta 1, completely inhibited T lymphocyte adhesion to the 80-kD fragment but had no effect on their attachment to the 38-kD fragment or to CS-1. Both alpha 4 beta 1 and alpha 5 beta 1 localized to focal adhesions when fibroblasts that express these receptors were grown on fibronectin-coated surfaces. These findings demonstrated a specific interaction of both receptors with fibronectin at focal contacts. In conclusion, these findings show clearly that cultured T lymphocytes use two independent receptors during attachment to fibronectin and that (a) alpha 5 beta 1 is the receptor for the RGD containing cell adhesion domain, and (b) alpha 4 beta 1 is the receptor for a carboxy-terminal cell adhesion region containing the Heparin II and IIICS domains. Furthermore, these data also show that T lymphocytes express a clear preference for a region of molecular heterogeneity in IIICS (CS-1) generated by alternative splicing of fibronectin pre-mRNA and that alpha 4 beta 1 is the receptor for this adhesion site.

PMID: 2527858 [PubMed - indexed for MEDLINE]



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A monoclonal antibody to VLA-4 alpha-chain (CDw49d) induce homotypic lymphocyte aggregation.

Bednarczyk JL, McIntyre BW.

Department of Immunology, University of Texas M.D. Anderson Cancer Center, Houston 77030.

The complex processes of cellular adhesion involve a variety of receptor to ligand interactions that are extremely important during the development of immune function. Lymphocyte activation by Ag or mitogen, CTL- and NK-mediated cytotoxicity, homing to lymphoid-associated tissue, and the attachment of lymphocytes to extracellular matrix proteins are all governed, at least in part, by cell surface adhesion receptors. During the analysis of mAb for the ability to block human cytotoxic T lymphocyte-mediated killing an inhibitory mAb was noted that caused rapid and vigorous aggregation among the CTL. This antibody, mAb L25, also induced aggregation among human T and B tumor cell lines. mAb L25 binds to an epitope on the alpha 4 subunit of the integrin protein VLA-4 and induced an adhesion event requiring divalent cations, energy, a fluid plasma membrane, and an intact cytoskeleton. The Ag-independent homotypic adhesion induced by mAb L25 was not inhibited by mAb to the lymphocyte function associated Ag-1 (CD11a/CD18), CD2, CD4, and CD8, or to their ligands ICAM-1, LFA-3, MHC class I, or MHC class II. We believe that these experiments suggest a role for VLA-4 in a novel system of leukocyte adhesion.

PMID: 2295817 [PubMed - indexed for MEDLINE]

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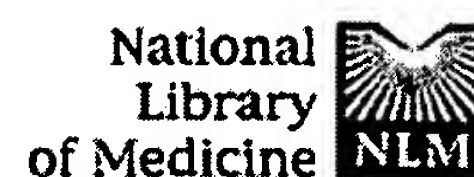
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Signaling by vascular cell adhesion molecule-1 (VCAM-1) through VLA-4 promotes CD3-dependent T cell proliferation.

Burkly LC, Jakubowski A, Newman BM, Rosa MD, Chi-Rosso G, Lobb RR.

Biogen, Inc., Cambridge, MA 02142.

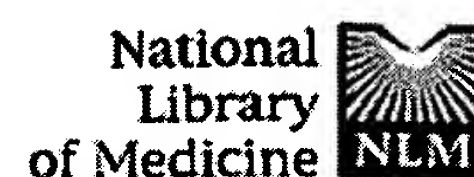
Vascular cell adhesion molecule, VCAM-1, is an adhesion molecule expressed on activated endothelium thought to play a role in leukocyte migration to sites of inflammation. VCAM-1 adheres to leukocytes through the VLA-4 integrin. Recombinant soluble VCAM-1 (rsVCAM) and anti-CD3 mAb OKT3 were utilized to address the role of the VCAM-1/VLA-4 pathway in antigen-dependent T cell activation. Monocyte-depleted T cells proliferated upon exposure to co-immobilized OKT3 and rsVCAM but to neither alone. In contrast, an anti-VLA-4 mAb HP1/2 failed to co-activate with OKT3, despite the fact that both rsVCAM and HP1/2 support T cell adhesion comparably. These data indicate that adhesive function is not sufficient for co-stimulatory activity. They also reveal that VCAM-1 may play a role in regulating T cell immune responses as well as migration in vivo.

PMID: 1718763 [PubMed - indexed for MEDLINE]

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Regulation of T cell proliferation by anti-CD49d and anti-CD29 monoclonal antibodies.

Bednarczyk JL, Teague TK, Wygant JN, Davis LS, Lipsky PE, McIntyre BW.

Department of Immunology, University of Texas M.D. Anderson Cancer Center, Houston 77030.

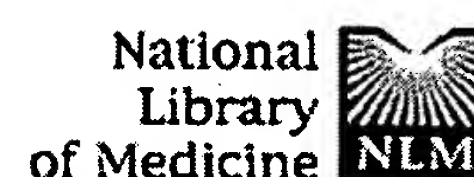
The beta 1 integrin VLA-4 (alpha 4 beta 1, CD49d/CD29), which is expressed on a large subpopulation of peripheral blood T lymphocytes, functions as a receptor for the endothelial adhesion protein VCAM-1 and the extracellular matrix protein fibronectin. Previous studies showed that immobilized fibronectin enhanced anti-CD3 monoclonal antibody (mAb)-induced T cell proliferation through binding to the integrins VLA-4 and VLA-5 (alpha 5 beta 1, CD49e/CD29). We studied the ability of the anti-CD49d mAb L25 to potentiate proliferation. T cell proliferation was induced by subthreshold concentrations of anti-CD3 mAb (mAb OKT3) coimmobilized with mAb L25 but not with coimmobilized anti-CD29 (beta 1) mAb. Soluble anti-CD29 mAb inhibited the proliferation induced by coimmobilized mAb OKT3 and L25 but not proliferation induced by mAb OKT3 with PMA or coimmobilized anti-CD26 mAb.

PMID: 1383369 [PubMed - indexed for MEDLINE]

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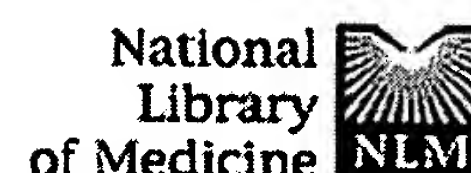
VLA-4 integrin on sarcoma cell lines recognizes endothelial VCAM-1. Differential regulation of the VLA-4 avidity on various sarcoma cell lines.

Mattila P, Majuri ML, Renkonen R.

Department of Bacteriology and Immunology, University of Helsinki, Finland.

Osteosarcomas and rhabdomyosarcomas are vigorously invading tumors. Before they can extravasate to the parenchymal organs and form metastases, they have to adhere to the endothelial cells lining the blood vessels and then penetrate through the endothelium. We show that several human sarcoma cell lines, osteosarcomas HOS, MG-63, U2-OS, and a rhabdomyosarcoma RD, express VLA-4 molecule on their surface and bind to the VCAM-I-expressing activated endothelial cell line Ea.hy 926. The increased sarcoma-cell adhesion could be abolished by treating the sarcoma cells with monoclonal antibodies (MAbs) VLA4 (both alpha- and beta-chain, HP2/1 and 4B4 respectively) or treating endothelial cells with VCAM-I antibody (4B9). Furthermore, we show that sarcoma cells adhere to recombinant soluble VCAM-I protein. On the other hand, these sarcoma cell lines do not express marked amounts of other ligands (such as CDII/18 or sialyl-Lex) for other endothelial adhesion molecules (ICAM-I, ICAM-2, E- and P-selectin) indicating that the VLA-4-VCAM-I dependent pathway might be of major importance in sarcoma extravasation. VLA-4 is not always in an avid form and therefore the expression of VLA-4 does not directly predict adherence to VCAM-I. The avidity of VLA-4 (measured by adherence to soluble VCAM-I) of MG-63 and U2-OS cells could be increased by a 30-min PMA treatment, whereas the avidity of VLA-4 on HOS cells increased only after 4 hr of PMA induction. Our results show that sarcoma cell lines (HOS, MG-63 U2-OS and RD) adhere to stimulated endothelium via VLA-4-VCAM-I adhesion molecules and that VLA-4 avidity on sarcoma cells can be differentially modulated by PMA.

PMID: 1281143 [PubMed - indexed for MEDLINE]

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A monoclonal antibody recognizing very late activation antigen-4 inhibits eosinophil accumulation in vivo.

Weg VB, Williams TJ, Lobb RR, Nourshargh S.

Department of Applied Pharmacology, National Heart and Lung Institute, London, UK.

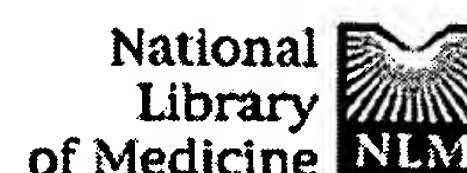
Using an in vivo test system, the role of the beta 1 integrin very late activation antigen-4 (VLA-4) in eosinophil accumulation in allergic and nonallergic inflammatory reactions was investigated. Eosinophil infiltration and edema formation were measured as the local accumulation of intravenously injected ¹¹¹In-labeled eosinophils and ¹²⁵I-human serum albumin. The inflammatory reactions investigated were a passive cutaneous anaphylaxis (PCA) reaction and responses elicited by intradermal soluble inflammatory mediators (platelet-activating factor, leukotriene B₄, C5a des Arg), arachidonic acid, and zymosan particles. The in vitro pretreatment of ¹¹¹In-eosinophils with the anti-VLA-4 monoclonal antibody (mAb) HP1/2, which crossreacts with guinea pig eosinophils, suppressed eosinophil accumulation in all the inflammatory reactions investigated. Eosinophil accumulation was inhibited to the same extent when mAb HP1/2 was administered intravenously. It is interesting that HP1/2 had no effect on stimulated edema formation. These results suggest a role for VLA-4 in eosinophil accumulation in vivo and indicate a dissociation between the inflammatory events of eosinophil accumulation and edema formation.

PMID: 8381157 [PubMed - indexed for MEDLINE]

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Attenuation of colitis in the cotton-top tamarin by anti-alpha 4 integrin monoclonal antibody.

Podolsky DK, Lobb R, King N, Benjamin CD, Pepinsky B, Sehgal P, deBeaumont M.

Gastrointestinal Unit, Massachusetts General Hospital, Boston 02114.

Recent studies have demonstrated the induced expression of endothelial adhesion molecules including E-selectin (also called endothelial leukocyte adhesion molecule-1), vascular cell adhesion molecule and intercellular adhesion molecule in actively involved mucosa of patients with ulcerative colitis and Crohn's disease. Similar induction has been demonstrated in the colon of the Cotton-top tamarin (CTT), a New World primate that experiences a spontaneous acute and chronic colitis resembling ulcerative colitis. To assess the potential importance of leukocyte adhesion as a necessary step in acute colitis, the effect of parenteral mAb directed against adhesion molecules on CTT colitis was evaluated in placebo-controlled blinded trials. Serial administration of either of two anti-E-selectin mAb designated BB11 and EH8 effectively coated endothelial surfaces expressing this vascular adhesion molecule. Although colitis activity was slightly diminished after the 10-d treatment period in CTT receiving either BB11 or EH8, this reduction was not significantly different than that seen in animals given a placebo control when assessed by a previously validated standardized scale of inflammatory activity: mean histologic activity grade 2.2 +/- 0.2 pretreatment vs 1.5 +/- 0.5 posttreatment in group receiving mAb and 2.1 +/- 0.1 pretreatment vs 1.3 +/- 0.5 posttreatment in the placebo group ($P > 0.2$). In contrast, administration of an anti-alpha 4 integrin mAb designated HP1/2 that binds VLA4 (alpha 4 beta 1) and presumably alpha 4 beta 7 integrins resulted in significant attenuation of acute colitis when compared to both pretreatment activity index ($P = 0.005$) and the placebo control group ($P < 0.01$): mean histologic activity grade 1.6 +/- 0.3 pretreatment vs 0.2 +/- 0.1 posttreatment in the group receiving HP1/2 and 1.8 +/- 0.5 pretreatment and 1.2 +/- 0.2 posttreatment in the placebo control group. These studies using a model of spontaneous colitis in the CTT demonstrate the feasibility of modulation of leukocyte-vascular adhesion and/or other integrin-mediated events possibly including T cell aggregation and T cell-stromal interactions, as well as lymphocyte homing. These results suggest both that these

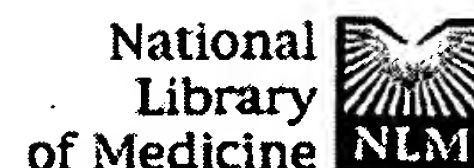
processes are important and possibly essential elements in sustaining acute colitis and that their disruption may result in therapeutic benefit.

PMID: 7686922 [PubMed - indexed for MEDLINE]

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Lymphocyte-endothelial interactions in inflamed synovia: involvement of several adhesion molecules and integrin epitopes

Fischer C, Thiele HG, Hamann A.

Abt. f. Immunologie, Medizinische Klinik, Universitätskrankenhaus Eppendorf, Hamburg, Germany.

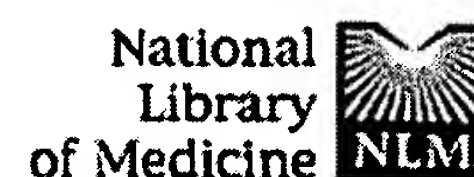
The role of several adhesion molecules for lymphocyte-endothelial interactions in the synovia of rheumatoid arthritis patients was studied using the frozen section assay. Partial inhibition of lymphocyte binding to endothelium of synovial sections could be observed with antibodies against CD44, L-selectin, and beta 1- and beta 2-integrins, pointing to the participation of several adhesion molecules in the regulation of lymphocyte immigration into inflamed synovia rather than the presence of a unique homing receptor. Different degrees of inhibition were found within a series of antibodies against alpha 4- and beta 1-integrins known to have functional effects in other interaction systems. In addition, increased binding to endothelial cells was induced when lymphocytes were pretreated with TS2/1 anti-beta 1 IgG, whereas binding to non-endothelial components of synovia was increased after treatment with HP 2/4 (anti-alpha 4) Fab. The data suggest a multifunctional role of alpha 4/beta 1-integrins in directly mediating adhesion as well as regulating adhesive interactions in the rheumatoid synovia.

PMID: 7688480 [PubMed - indexed for MEDLINE]

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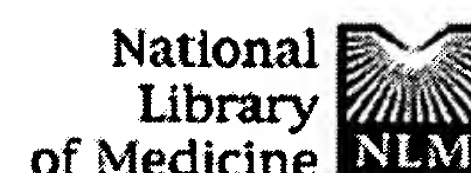
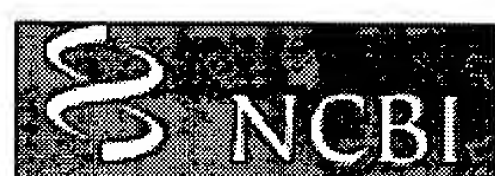
Lymphocyte locomotion in three-dimensional collagen gels. Comparison of three quantitative methods for analysing cell trajectories.

Friedl P, Noble PB, Zanker KS.

Institut für Immunologie, Naturwissenschaftliche Fakultät, Universität Witten, Herdecke, Germany.

We evaluated three different quantitative evaluation methods for lymphocyte locomotion in three-dimensional collagen gels: (1) the length of the two-dimensional migration path (distance migrated) was compared to (2) the resulting average displacement from the starting to the end point and (3) the displacement of the furthest migrating population (cells with high displacement). Locomotion of immunomagnetically isolated human CD4⁺ and CD8⁺ peripheral blood lymphocytes suspended in type I collagen gels was recorded using time-lapse videomicroscopy. Paths of randomly selected locomoting cells were digitized, reconstructed and quantitatively analysed. For spontaneously locomoting CD4⁺ and CD8⁺ lymphocytes (90 min observation period) the mean total distance migrated was 10.0 +/- 3.7 microns/min (CD4⁺; n = 114 cells) and 5.6 +/- 3.3 microns/min (CD8⁺; n = 90 cells). The mean displacement from the individual starting point amounted to 1.3 +/- 0.7 micron/min for CD4⁺ and 1.1 +/- 0.7 micron/min for CD8⁺ cells, thus representing only 5-25% of the total migration path (index range displacement/distance migrated: 0.13-50%). Incubation with interleukin-8 and/or receptor blocking by monoclonal antibodies against VLA-2 (Gi9) or VLA-4 (HP2/1) integrins significantly altered the mean length of the migration paths for six out of ten different experimental conditions. Average displacement or displacement of the most active cells detected significant changes in two and three out of ten samples. Whereas the interleukin-8 induced locomotory changes were correctly represented by end point determination, relatively slight but significant modulation in lymphocyte behaviour by anti-integrin antibodies was revealed solely by analysis of the complete cell trajectory. In conclusion, the cell trajectory may represent a sensitive method for evaluating induced subtle changes in lymphocyte locomotory characteristics.

PMID: 7901283 [PubMed - indexed for MEDLINE]

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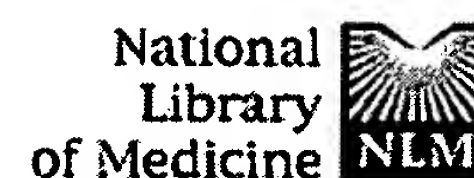
Adhesion to fibronectin primes eosinophils via alpha 4 beta 1 (VLA-4).

Anwar AR, Walsh GM, Cromwell O, Kay AB, Wardlaw AJ.

Department of Allergy and Clinical Immunology, National Heart & Lung Institute, London.

Human peripheral blood eosinophils adhered specifically to microtitre plates coated with plasma fibronectin (Fn) in a dose- and time-dependent fashion. Adhesion was optimal at 60 min at a concentration of 100 micrograms/ml. Adherence to Fn was up-regulated by platelet-activating factor (PAF; optimum concentration of 10^{-6} M) and was significantly inhibited by a polyclonal anti-Fn antibody ($P < 0.05$). The following evidence suggested that eosinophil adhesion to Fn was mediated by alpha 4 beta 1: (1) eosinophil adherence to Fn was not inhibited by an Arg-Gly-Asp-Ser (RGDS) synthetic peptide; (2) there was a dose-dependent adherence of eosinophils to microtitre plates coated with the 40,000 MW proteolytic fragment of Fn that contains the CS-1 alpha 4 beta 1 binding region, whereas adherence to the 120,000 MW chymotryptic fragment of Fn, which contains the RGD-dependent binding site, was weak and only observed at high concentrations (> 250 micrograms/ml); (3) significant inhibition of eosinophil adherence to Fn was achieved by monoclonal antibodies (mAb) against the alpha chain of VLA-4 but not by a mAb against CD45 or a mouse myeloma antibody as negative controls. After adhesion to Fn, eosinophils were investigated for their capacity to release leukotriene C4 in response to stimulation with a suboptimal concentration of calcium ionophore (2×10^{-6} M). Significant enhancement of release was detected with Fn-coated plates but not with the control bovine serum albumin (BSA) ($P < 0.01$). Furthermore, this enhancement was significantly inhibited by the alpha 4 beta 1 mAb HP2/1 ($P < 0.05$) but not by an anti-CD45 mAb. From these studies we conclude that (1) alpha 4 beta 1 (VLA-4) integrin is a major receptor for Fn on human eosinophils and (2) adhesion to Fn may prime eosinophils for mediator release during allergic inflammation.

PMID: 7927493 [PubMed - indexed for MEDLINE]



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Prevention of mercuric chloride-induced nephritis in the brown Norway rat by treatment with antibodies against the alpha 4 integrin.

Molina A, Sanchez-Madrid F, Bricio T, Martin A, Barat A, Alvarez V, Mampaso F.

Department of Pathology, Ramon and Cajal Hospital, Madrid, Spain.

HgCl₂ induces the synthesis of anti-GBM Abs with the development of glomerular and interstitial nephritis, as well as proteinuria, in the Brown Norway rat. The development of this autoimmune disease is a consequence of the appearance of an autoreactive T cell subset-inducing activation of B cells. The administration to mercury-treated rats of the mouse anti-human VLA alpha 4 HP2/1 mAb, which cross-reacts with the rat homologue integrin, completely abrogated the interstitial cell infiltrates. As demonstrated by peripheral blood analysis, this effect is not a result of the depletion of circulating leukocytes or leukocyte subsets. Interestingly, the administration of Abs specific for the alpha 4 integrin also highly reduced anti-GBM Ab synthesis, thus preventing detectable glomerular deposits and proteinuria. Our results confirm that in vivo alpha 4 functions in adhesive interaction of circulating leukocytes and vascular endothelium, and is centrally important in the extravasation and migration of T lymphocytes to sites of tissue injury. We also found a complete absence of interstitial cell infiltrates, together with a positive glomerular IgG linear deposition pattern, when anti-GBM Abs were passively transferred to rats pretreated with anti-alpha 4 mAb, thus indicating an independent role of alpha 4 integrin in both extravasation of immune cells and production of autoantibodies. Furthermore, these in vivo findings provide preliminary evidence for the participation of the VLA-4 integrin in mediating the intercellular interaction of leukocytes regulating the production of Abs, most likely through the existence of additional yet unknown ligand(s).

PMID: 8051427 [PubMed - indexed for MEDLINE]

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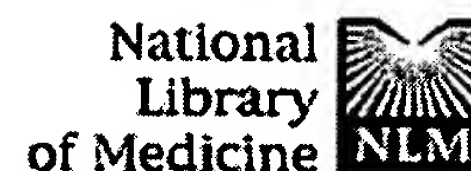
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☐ 1: J Biol Chem. 1994 Mar 18; 269(11): 8348-54.[Related Articles, Link](#)FREE full text article at
www.jbc.org**Identification of a combinatorial epitope expressed by the integrin alpha 4 beta 1 heterodimer involved in the regulation of cell adhesion.****Bednarczyk JL, Szabo MC, Wygant JN, Lazarovits AI, McIntyre BW.**

Department of Immunology, University of Texas M. D. Anderson Cancer Center, Houston 77030.

The alpha 4 integrin subunit can associate with either the beta 1- or beta 7- integrin subunit to form two unique adhesion receptors alpha 4 beta 1 and alpha 4 beta 7. We developed a monoclonal antibody (mAb 19H8) that immunoprecipitated alpha 4 beta 1, induced homotypic leukocyte aggregation, and blocked the binding of cells to a synthetic peptide corresponding to the CS-1 peptide region of fibronectin. Aggregation cross-blocking analysis suggested that mAb 19H8 belonged to the group of mAbs that react with the B2 epitope of the alpha 4 subunit (alpha 4.B2 epitope); however, unlike the alpha 4.B2-specific mAb L25, mAb 19H8 did not immunoprecipitate alpha 4 beta 7. In addition, mAb 19H8 did not bind to beta 1-positive cells unless transfected with alpha 4 cDNA. These results indicate that mAb 19H8 was not specific for an individual alpha 4, beta 1, or beta 7 subunit but reacted with an epitope formed from the association of alpha 4 with beta 1. Separating the alpha 4 from the beta 1 subunit, by removing divalent cations or by treatment with high pH, disrupted mAb 19H8 binding. In contrast, the alpha 4-specific mAb L25 and the beta 1-specific mAb 18D3 could react with their respective subunits without subunit association. Therefore, mAb 19H8 defined a novel regulatory epitope expressed by the integrin alpha 4 beta 1.

PMID: 7510686 [PubMed - indexed for MEDLINE]

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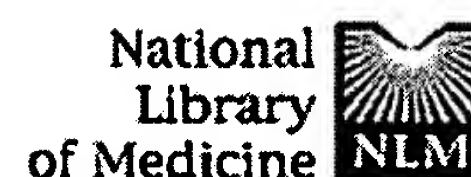
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A fluorescent cellular adhesion assay using insect cell produced human VCAM1.

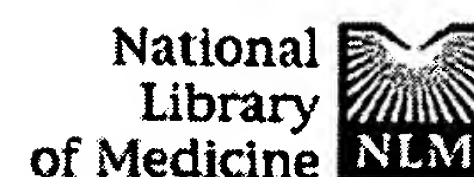
Stoltenborg JK, Tsao PW, George HJ, Bouchard PJ, Wexler EJ, Hausner EA.

Department of Cardiovascular Diseases, Du Pont Merck Pharmaceutical Company, Wilmington, DE 19880-0400.

Activated endothelium and some dendritic cells express the adhesion molecule VCAM1, a member of the immunoglobulin gene superfamily. Mononuclear leukocytes display the integrin VLA4 that functions as a counterreceptor for VCAM1. The interaction of VCAM1 with VLA4 mediates cell to cell adhesion events believed to be important regulators of inflammation, cancer cell metastasis, and atherosclerosis. This report describes the development of a fluorescent adhesion assay that specifically measures T cell adhesion to recombinant human VCAM1 (rVCAM1) expressed in a baculovirus expression vector system (BEVS). We describe a simple and rapid protocol to partially purify non-denatured rVCAM1 from insect cell membrane preparations (VCAM1 infected Sf9 cells). Jurkat cells, T cell line expressing VLA4, specifically adhered to the rVCAM1 membrane preparations coated onto 96-well plates. Jurkat cells did not adhere to control membrane preparations that lacked rVCAM1 protein. Both unstimulated and IL-2 stimulated Jurkat cells displayed functional VLA4 capable of binding to immobilized rVCAM1. Monoclonal antibodies recognizing either VCAM1 (E1/6, BBA6) or VLA4 (HP2/1) blocked specific VCAM1/VLA4 adhesion, whereas a monoclonal antibody to the alpha chain of LFA1 did not block adhesion. The methods described here could be applied to develop similar functional assays for other cell surface receptors/counterreceptors expressed in a BEVS.

PMID: 7523526 [PubMed - indexed for MEDLINE]

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Erratum in:

- Biochem J 1996 Aug 1;317(Pt 3):959.

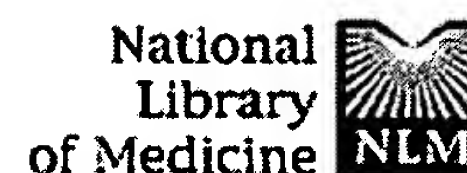
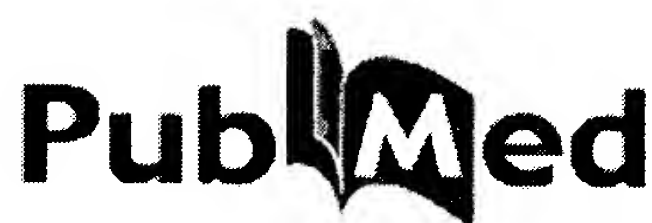
Identification of putative ligand-binding sites of the integrin alpha 4 beta 1 (VLA-4, CD49d/CD29)

Kamata T, Puzon W, Takada Y.

Department of Vascular Biology, Scripps Research Institute, La Jolla, CA 92037, USA.

Integrin alpha 4 beta 1 recognizes both fibronectin (CS-1 sequence) and vascular cell adhesion molecule-1 (VCAM-1). To localize the ligand-binding sites of alpha 4, we located the epitopes for function-blocking anti-alpha 4 monoclonal antibodies (mAbs), including those that recognize previously described (but not yet physically localized) functional epitopes (A, B1, B2 and C) using interspecies alpha 4 chimeras expressed in mammalian cells. Epitopes B1 and B2 were associated with ligand binding, and epitopes A and B2 with homotypic cellular aggregation. mAbs P4C2 (epitope B2), 20E4 and PS/2 were mapped within residues 108-182; mAbs HP2/1 (epitope B1), SG/73 and R1-2 within residues 195-268; mAbs HP1/3 (epitope A) and P4G within residues 1-52; and B5G10 (epitope C) within residues 269-548. The data suggest that residues 108-268, which do not include bivalent-cation-binding motifs, are related to VCAM-1 and CS-1 binding, and more N-terminal portions of alpha 4 (residues 1 and 52 and 108-182) to homotypic aggregation. Since mAbs PS/2 and HP2/1 block alpha 4 beta 7 binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), the MAdCAM-1-binding site is close to, or overlapping with, VCAM-1- and CS-1-binding sites. The role of Asp-130 of beta 1 in the binding to VCAM-1 and CS-1 peptide was examined. Chinese hamster ovary (CHO) cells expressing beta 1 (D130A) (Asp-130 to Ala mutant of beta 1) and alpha 4 showed much less binding to both ligands than CHO cells expressing wild-type beta 1 and alpha 4 [a dominant negative effects of beta 1 (D130A)], suggesting that Asp-130 of beta 1 is critical for binding to both ligands and that the two ligand share common binding mechanisms [corrected].

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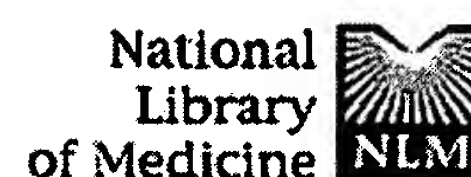
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FULL-TEXT ARTICLE**The novel recognition site in the C-terminal heparin-binding domain of fibronectin by integrin alpha 4 beta 1 receptor on HL 60 cells.****Mohri H, Katoh K, Iwamatsu A, Okubo T.**

First Department of Internal Medicine, Yokohama City University School of Medicine, Japan.

The hematopoietic cell recognition sites of human fibronectin (FN) are the Arg-Gly-Asp-Ser (RGDS) sequence recognized by widely distributed integrin receptor alpha 5 beta 1 and the type III connecting segment (III CS) containing two cell-binding sites, designated CS1 and CS5, that are recognized by the alpha 4 beta 1 receptor. The C-terminal heparin-binding domain of FN (Hep II) has recently been demonstrated to support adhesion of alpha 4 beta 1-dependent melanoma cells [A. P. Mould and M. J. Humphries (1991) EMBO J. 10, 4089-4095]. Previously we demonstrated that this region of FN mediated binding of FN to HL-60 cells (acute promyelocytic leukemia cell line) by direct interaction independently of RGD and CS1 [H. Fujita et al., (1995) Exp. Cell Res. 217, 484-488]. In this study we have characterized a novel site in the Hep II region for binding to HL-60 cells. alpha 4 beta 1 and alpha 5 beta 1 were expressed on HL-60 cells, while alpha 2 beta 1 and alpha 3 beta 1 were not present, as shown by flow cytometry using monoclonal antibodies specific for the different integrins. Anti-alpha 4 beta 1 (P4C2) and anti-beta 1 (JB1a) antibodies inhibited binding of a 29-kDa dispase-digestive fragment of FN to HL-60 cells. This fragment contains the C-terminal heparin-binding domain of FN but lacks CS1 and CS5. Only the peptide representing the sequence from Val1866 to Arg1880, designated E1, inhibited the binding of the 29-kDa fragment to HL-60 cells. The active region of this peptide was a sequence of Thr-Asp-Ile-Asp-Ala-Pro-Ser (TAI-DAPS), which is homologous to Leu-Asp-Val-Pro-Ser (LDVPS) derived from the active site of CS1. Furthermore, labeled E1 peptide directly bound to HL-60 cells. The anti-alpha 4 beta 1 antibody (P4C2) inhibited this interaction. These results indicate that the site of binding to hematopoietic cells is present in the Hep II region of FN and the definition of the chemical structure of FN clarifies a fundamental mechanism of cell invasion of the extracellular matrix.

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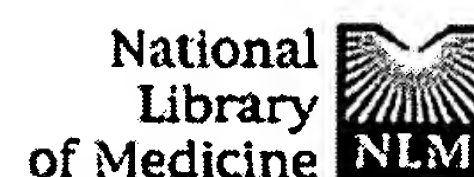
Lymphocyte adhesion to endothelium derived from human lymphoid tissue.

Castro A, Bono MR, Simon V, Roseblatt M.

Departamento de Biología, Facultad de Ciencias, Universidad de Chile, Santiago/Chile.

The development of an efficient immune response depends on the capacity of antigen-specific lymphocytes to migrate into secondary lymphoid organs. The first step in the process of lymphocyte extravasation involves lymphocyte binding to the vascular endothelium. Although several adhesion receptors have been implicated in the migration of lymphocytes to inflamed tissue, their role in the extravasation of these cells to normal lymphoid organs is not yet clearly established. The involvement of adhesion molecules in lymphocyte entrance to secondary lymphoid organs can be better assessed in an in vitro system using endothelial cells in culture. Here we report on the isolation and culture of a homogeneous population of adherent cells of endothelial origin derived from human tonsils (TEC) and on adhesion studies performed with these cells. Beginning from primary cultures of human tonsils, we isolated a population of cells that we show by FACS analysis to present the intracellular endothelial cell marker Von Willebrand factor and LVAP-2, a surface molecule present in venules from lymphoid organs. The cells are negative for FDC, IDC and macrophage markers. They express ICAM-1, VCAM-1 and CD40 both constitutively and in inducible forms and are induced by IFN-gamma to express major histocompatibility complex class II antigens. As opposed to endothelial cells from human umbilical cord (HUVEC), they do not need to be activated by cytokines to bind lymphoid cells via VLA-4. The mAb HP2/1 directed to the integrin VLA-4 blocks adhesion of Ramos and Daudi cells to tumor necrosis factor alpha (TNF-alpha)-treated HUVEC and to untreated TEC but not of tonsil-derived MNC. On the other hand, an anti-VCAM-1 antibody that blocks adhesion of Ramos and Daudi cells to TNF-alpha-treated HUVEC, does not block adhesion of these cells to TEC, suggesting the presence on the tonsillar endothelial cells of a ligand for VLA-4 different from VCAM-1. We show here that this ligand is not fibronectin.

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Specific inhibition of T lymphocyte coactivation by triggering integrin beta 1 reveals convergence of beta 1, beta 2, and beta 7 signaling pathways.

Woodside DG, Teague TK, McIntyre BW.

Department of Immunology, University of Texas, M.D. Anderson Cancer Center, Houston 77030, USA.

T cell coactivation is a dynamic process subject to integrin-dependent positive and negative regulation. Costimulation of human peripheral blood T cells by CD3 mAb OKT3 in conjunction with anti-alpha 4 has been shown to be down-regulated by the anti-beta 1.1 epitope-specific mAb 18D3. As expected, maximal costimulation induced by alpha 4-specific mAb L25 was inhibited (70%) by the addition of soluble mAb 18D3. Surprisingly, soluble mAb 18D3 inhibited maximal proliferation induced by the costimulatory alpha 4 beta 7-specific mAb ACT-1 by 40%, thus demonstrating that one integrin subfamily can regulate the activity of another. To determine whether mAb 18D3 could regulate more than alpha 4-associated integrin-mediated costimulation, non-alpha 4 integrins were tested. mAb 18D3 inhibited maximal proliferation induced by alpha 4-specific mAb 3D6, and an alpha 4-specific mAb 16. This clearly demonstrates that a variety of integrin costimulatory molecules (of the beta 1, beta 2, and beta 7 subfamilies) can be regulated negatively by mAb 18D3. To analyze the specificity of this negative regulation, other cell surface costimulatory molecules were tested for susceptibility to mAb 18D3. Although Abs specific for CD4, CD26, CD28, CD44, CD45RA, or CD45RO were sufficient to activate T cells when co-immobilized with anti-CD3 mAb, all were refractory to the inhibitory effects of mAb 18D3. Inhibition of T cell activation directly correlated with diminished IL-2 production. This suggests that mAb 18D3 selectively regulates integrin-dependent T cell activation by delivering a negative effect at some common point utilized by various integrin subfamilies.

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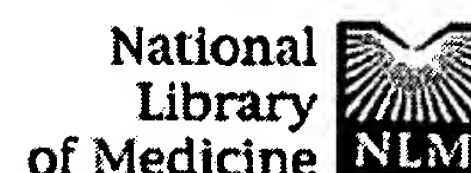
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Effect of interleukin-5 exposure during in vitro eosinophilopoiesis on MAC-1 adhesion molecule expression and function on cultured human eosinophils.

Hamann KJ, Neeley SP, Dowling TL, Grant JA, Leff AR.

Department of Medicine, University of Chicago, IL 60637, USA.

We examined the selective effects of interleukin (IL-5) in regulating the maturational expression of surface adhesion molecules on human eosinophils and adhesion to endothelial cells during eosinophilopoiesis in vitro.

Expression of the beta 2 integrins (CD11/CD18) and the beta 1 integrin, VLA-4 (CD49d/CD29), was assessed during development in culture with IL 3, IL-5, and granulocyte-macrophage colony stimulating factor in cultures of human umbilical cord blood-derived eosinophil (CDE) precursor cells.

Expression of both CD11b and CD18 subunits of Mac-1 was lower on CDE which were continuously (= chronically) exposed to IL-5 than on CDE which were cultured without IL-5 for the final week of culture. CD11b expression on cells grown without IL-5 was 71.3 +/- 5.92 (mean specific fluorescence value [MSF] as measured by flow cytometry) versus 52.5 +/- 4.48 MSF for Mac-1 alpha (CD11b) on CDE grown in the continued presence of 2 x 10⁻¹ mol/L IL-5 (P < .01). Although expression of VLA-4 decreased as CDE matured, expression of CD29 and CD49d were similar regardless of cytokine exposure for the final week of culture. For eosinophils cultured without IL-5, acute stimulation with 10⁻⁸ mol/L IL-5 increased CD11b surface expression and increased the number of cells adhering to unstimulated human umbilical vein endothelial cells (HUVEC) from 4,570 +/- 780 cells (9.14 +/- 1.56% adhesion) to 8,385 +/- 515 cells (16.8 +/- 1.03% adhesion) (P < .01). Basal adhesion to unstimulated HUVEC of CDE cultured continuously with IL-5 was comparable (8.62 +/- 1.12% adhesion; P = NS), but neither CD11b expression (50.3 +/- 11.8 MSF; P = NS v control) nor adhesion to HUVEC (6.77 +/- 1.35%; P = NS) was enhanced in these eosinophils after acute stimulation with IL-5. Blockade of adhesion to IL-1-stimulated HUVEC caused by the anti-CD49d monoclonal antibody (MoAb), HP2/1, was comparable for cells cultured with IL-5 and without IL-5. However, the anti-CD18 MoAb, R15.7, caused 47.6 +/- 5.08% inhibition of adhesion of eosinophils cultured without IL-5 and only 25.8 +/- 5.20% for cells cultured continuously with IL-5 (P < .01), and failed to block significantly the

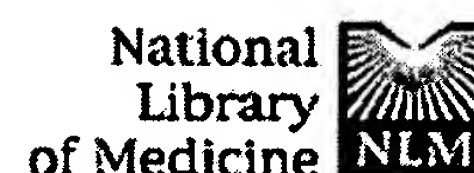
adhesion of only the latter cells to IL-4-stimulated HUVEC. Our data show that continuous, chronic exposure to low concentrations of IL-5 causes decreased expression of Mac-1 and refractoriness to acute stimulation with IL-5 of adhesion to HUVEC. These data further demonstrate that CDE maturing in the continued presence of IL-5 adhere to HUVEC predominantly through VLA-4 ligation.

PMID: 8896426 [PubMed - indexed for MEDLINE]

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Phorbol ester stimulation increases sickle erythrocyte adherence to endothelium: a novel pathway involving alpha 4 beta 1 integrin receptors on sickle reticulocytes and fibronectin.

Kumar A, Eckmam JR, Swerlick RA, Wick TM.

School of Chemical Engineering, Georgia Institute of Technology, Atlanta 30332-0100, USA.

Sickle-cell adherence to endothelium has been hypothesized to initiate or contribute to microvascular occlusion and pain episodes. Adherence involves plasma proteins, endothelial-cell adhesion molecules, and receptors on sickle erythrocytes. It has previously been reported that sickle reticulocytes express the alpha 4 beta 1 integrin receptor and bind to cytokine-activated endothelium via an alpha 4 beta 1/vascular-cell adhesion molecule-1 (VCAM-1) interaction. To elucidate other roles for alpha 4 beta 1 in sickle-cell adherence, the ability of activated alpha 4 beta 1 to promote adhesion to endothelium via a ligand different than VCAM-1 was explored. Adherence assays were performed under dynamic conditions at a shear stress of 1 dyne/cm². Preincubation of sickle erythrocytes with phorbol 12,13-dibutyrate (PDBu) increased adherence of sickle cells eightfold as compared with untreated sickle cells. Normal erythrocytes, whether treated with PDBu or not, did not adhere to the endothelium. Activating anti-beta 1 antibodies 4B4 and 8A2 also increased the adhesion of sickle, but not normal, red blood cell (RBC) adhesion to endothelium. Anti-alpha 4 antibodies HP1/2 and HP2/1, inhibitory antibody 4B5, or an RGD peptide inhibited sickle-cell adherence induced by PDBu. Additional studies were undertaken to examine if fibronectin, a ligand for activated alpha 4 beta 1, was involved in PDBu-induced sickle erythrocyte adherence. Adherence of PDBu-treated sickle cell was completely inhibited by the CS-1 peptide of fibronectin. Fibronectin was detected on the surface of washed endothelium using an antifibronectin antibody in enzyme-linked immunosorbent assays. Antifibronectin antibody pretreatment of endothelial cells inhibited PDBu-induced adherence by 79% +/- 17%. Incubation of sickle RBCs with exogenous fibronectin after PDBu treatment inhibited adherence 86% +/- 8%. Taken together, these data suggest that endothelial-bound fibronectin mediates adherence of PDBu-treated sickle cells. Interleukin-8 (IL-8), a chemokine released in response to bacterial infection, viral infection, or other injurious agents, and known to activate

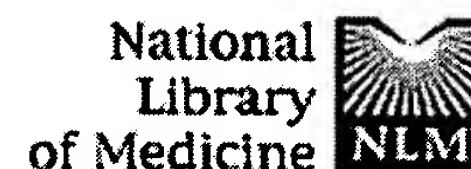
integrins, also increased adherence of sickle erythrocytes to endothelial cells via fibronectin. This novel adherence pathway involving sickle-cell alpha 4 beta 1 activated by PDBu or IL-8 may therefore be relevant in vivo at vascular sites that produce IL-8 or similar agonists in response to vascular injury or immune activation. These observations describe ways in which inflammation and immune responses cause vasoocclusive complications in sickle-cell disease.

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Regulation of human T lymphocyte coactivation with an alpha4 integrin antagonist peptide.

McIntyre BW, Woodside DG, Caruso DA, Wooten DK, Simon SI, Neelamegham S, Revelle JK, Vanderslice P.

Department of Immunology, University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.

The cyclic hexapeptide CWLDVC (TBC 772) is an antagonist of alpha4 integrins and a potent inhibitor of lymphocyte interactions with fibronectin, vascular cell adhesion molecule-1, and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). As such, peptide TBC 772 effectively inhibits the activation of freshly isolated human T lymphocytes stimulated with purified vascular cell adhesion molecule-1 coimmobilized with anti-CD3 mAb. The influence of peptide binding on distinct sites of the alpha4beta1 complex was determined by flow cytometry and cellular adhesion assays employing a panel of mAbs. Binding of the alpha4-specific mAb L25 and the beta1-specific mAb 33B6 was not altered by the peptide; however, binding of mAb 19H8, which is specific for a combinatorial epitope of alpha4beta1, was dramatically inhibited. Treatment of lymphocytes with the peptide caused an increase in a ligand-induced epitope on beta1 integrin defined by mAb 15/7. In T cell activation studies using coimmobilized anti-CD3 mAb and the anti-integrin mAbs, the peptide had broader inhibitory activity, suppressing costimulation induced by all the integrin mAbs. The peptide was not generally toxic and was integrin selective in its suppressive activity, as coactivation by ligation of CD3 in conjunction with CD28 or CD26 was not affected. These results suggest that the antagonist peptide CWLDVC can effectively neutralize integrin coactivation systems by a mechanism independent of competitive binding.

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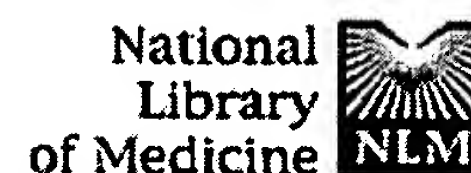
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www.bloodjournal.org**Tumor necrosis factor alpha-induced eosinophil accumulation in rat skin is dependent on alpha4 integrin/vascular cell adhesion molecule-1 adhesion pathways.****Sanz MJ, Hartnell A, Chisholm P, Williams C, Davies D, Weg VB, Feldmann M, Bolanowski MA, Lobb RR, Nourshargh S.**

National Heart and Lung Institute, Imperial College School of Medicine, London, UK.

Tumor necrosis factor alpha (TNFalpha) is a cytokine implicated in the pathogenesis of numerous chronic and acute inflammatory conditions. In the present study, we have characterized the ability of TNFalpha in inducing eosinophil accumulation in rat skin and have shown the inhibitory effects of anti-alpha4 integrin and anti-vascular cell adhesion molecule-1 (VCAM-1) antibodies on this response. The intradermal injection of recombinant human TNFalpha induced a slowly developing, dose-dependent accumulation of ¹¹¹In-eosinophils in rat skin that was maximal at the dose of 10(-11) mol/site. Coadministration of TNFalpha with the soluble TNFalpha receptor (p55)-IgG fusion protein (TNFR-IgG) totally inhibited the ¹¹¹In-eosinophil accumulation induced by the cytokine. The TNFalpha-induced ¹¹¹In-eosinophil accumulation was not affected after pretreatment of rats with the platelet-activating factor (PAF) receptor antagonist UK-74,505 or the antihuman interleukin-8 monoclonal antibody (MoAb) DM/C7. In contrast, the intravenous administration of an anti-alpha4 integrin MoAb, HP2/1 (3.5 mg/kg), or an anti-VCAM-1 MoAb, 5F10 (2 mg/kg), greatly inhibited the ¹¹¹In-eosinophil accumulation induced by TNFalpha (the responses detected at 10(-11) mol/site were inhibited by 78% and 50%, respectively). These results show that TNFalpha is an effective inducer of eosinophil accumulation in vivo, with this response being dependent on an interaction between alpha4 integrins and VCAM-1.

PMID: 9354685 [PubMed - indexed for MEDLINE]

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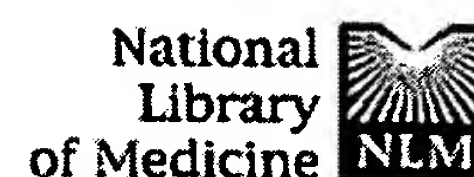
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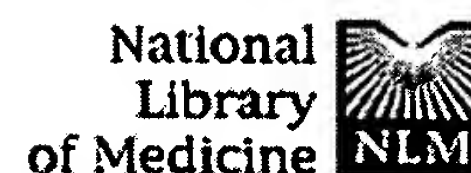
Differential effects of antibodies to vascular cell adhesion molecule-1 and distinct epitopes of the alpha4 integrin in HgCl₂ induced nephritis in Brown Norway rats.

Escudero E, Nieto M, Martin A, Molina A, Lobb RR, Sanchez-Madrid F Mampaso F.

Department of Pathology, Hospital Ramon y Cajal, Universidad de Alcala, Madrid, Spain.

Four distinct epitopes (A, B1, B2, and C) have been functionally defined on the human alpha4 integrin. In this study, two cross-reactive antihuman alpha4 monoclonal antibodies (mAb) (HP2/1 and HP2/4 specific for epitopes B1 and B2, respectively) were used to functionally characterize the rat VLA-4 subunit and to define similar functional epitopes in this rodent species. It was found that B1 and B2 anti-alpha4 mAb completely block adhesion to fibronectin, but the inhibition of adhesion to vascular cell adhesion molecule 1 (VCAM-1) with HP2/1 mAb was lower than with HP2/4 mAb. It was also observed that epitope B2 HP2/4 mAb induced homotypic aggregation in rat lymphocytes, whereas epitope B1 HP2/1 mAb did not. Using the HgCl₂ model of nephritis, this study shows the protective effect of both anti-alpha4 mAb against infiltration of the renal interstitium by leukocytes. Nevertheless HP2/1 mAb, but not HP2/4 mAb, virtually abolished the anti-glomerular basement membrane antibody synthesis and glomerular deposits. These findings indicate the dual but independent role played by alpha4 integrins in both extravasation of leukocytes and in the production of antibodies. Finally, this study demonstrates that anti-rat VCAM-1 mAb showed a positive reactivity of the renal vascular endothelium and, most importantly, that administration of anti-VCAM-1 antibodies completely abrogated the interstitial cell infiltrates without affecting anti-glomerular basement membrane antibody production. These results confirm the important role played by VLA-4/VCAM-1 pathway in leukocyte infiltration, and further support the dual and independent role of alpha4 integrins in both renal infiltration and autoantibody synthesis in this model of renal disease.

PMID: 9773789 [PubMed - indexed for MEDLINE]



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Differential leukocyte recruitment from whole blood via endothelial adhesion molecules under shear conditions.

Reinhardt PH, Kubes P.

Immunology Research Group, University of Calgary, Calgary, Alberta, Canada.

The objective of this study was to determine if vascular cell adhesion molecule (VCAM-1), E-selectin, and P-selectin could selectively recruit leukocyte subpopulations, and whether this was affected by shear force or adhesion molecule concentration. Cover slips coated with purified adhesion molecules were incorporated into laminar flow chambers. Whole human blood was perfused for 5 minutes over these cover slips at relative shear forces of 2 to 40 dynes/cm². Chasing the whole blood with buffer permitted visualization of leukocyte-substratum interactions. Leukocytes were observed to roll on and adhere to VCAM-1 at shears between 2 and 15 dynes/cm². As assessed by cover slip staining, the majority of these cells were lymphocytes, but eosinophils, monocytes, and, surprisingly, neutrophils were also recruited. Events inhibitable by anti-4-integrin antibody (HP1/2). Neutrophils were effectively recruited onto the selectins, with interactions occurring at shears as high as 30 and 40 dynes/cm² for E- and P-selectin respectively. Eosinophils had high affinity for P- but not E-selectin. Mononuclear cells did not have high affinity for either selectin, but interacted avidly with VCAM-1. Antibodies against P-selectin (G1) and E-selectin (ES-1) completely blocked interactions on these substrates. Reducing the concentration of adhesion molecules did not appreciably change recruitment patterns except for VCAM-1, where neutrophils were no longer recruited. The novel use of whole blood in flow chambers shows a partial selectivity of selectins and VCAM-1 for certain subpopulations of leukocytes under varying physiologic shear conditions.

PMID: 9845535 [PubMed - indexed for MEDLINE]

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